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A Comprehensive Review for Sepsis and Septic Shock Management in The Emergency Room

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Abstract

Sepsis and septic shock are life-threatening conditions characterized by organ dysfunction resulting from a dysregulated host response to infection. The management of septic patients represents a significant challenge for emergency physicians, as early recognition and prompt initiation of treatment are crucial for improving patient outcomes. This narrative review provides an updated and comprehensive overview of the pathophysiology and management of septic shock, focusing on recent advancements and practical implications for emergency physicians. The review discusses the hemodynamic alterations in septic shock, including macrocirculatory and microcirculatory derangements, and their impact on oxygen delivery and tissue perfusion. The cornerstone of initial treatment for septic shock patients is fluid therapy, and the review explores the current debates surrounding fluid volume, choice of fluids, and the use of dynamic tests to guide fluid responsiveness. The early administration of vasopressors, particularly norepinephrine, is also highlighted as a key intervention to counteract the severely impaired arterial tone in septic shock. The review emphasizes the importance of timely antimicrobial therapy, discussing the timing of administration, selection of appropriate agents, and considerations for dosing in the emergency department setting. Additionally, the potential roles of adjunctive therapies, such as corticosteroids, ascorbic acid, and thiamine, are examined in light of recent clinical trials and meta-

analyses. The review concludes by stressing the importance of a systematic approach to the early identification and management of septic patients in the emergency department, tailored to the specific characteristics of each patient, to reduce mortality and improve outcomes.
Keywords: septic shock, sepsis, emergency room

Introduction

The management of septic patients represents a significant challenge for emergency physicians. Sepsis is a life-threatening condition characterized by organ dysfunction resulting from a dysregulated host response to infection. A severe subset of this condition, septic shock, involves circulatory, cellular, and metabolic abnormalities that contribute to elevated mortality rates (Singer et al., 2016). According to the Sepsis-3 definitions, the identification of septic patients has been standardized using a new algorithm incorporating the Sequential Organ Failure Assessment (SOFA) and quick-SOFA scores. Guidelines from the 2016 Surviving Sepsis Campaign (SCC) provide recommendations for the management of sepsis; however, the 2018 SCC Bundle update emphasized the critical need for prompt initiation of resuscitation procedures within the first hour, referred to as the hour-1 bundle (Levy et al., 2018). Given that sepsis is a time-sensitive condition, and that initial medical contact often occurs in the Emergency Department (ED), early recognition and risk stratification are essential. Numerous prognostic markers have been identified to aid emergency physicians in implementing more aggressive and effective management strategies. Nevertheless, in-hospital mortality remains alarmingly high, with rates reaching up to 40% in Europe and North America (Vincent et al., 2019).

This narrative review aims to outline the primary pathophysiological characteristics of sepsis and septic shock while providing an in-depth discussion of recent advancements in their initial management.

Hemodynamic Alterations

From a hemodynamic standpoint, septic shock involves concurrent disruptions at the macrocirculatory and microcirculatory levels, resulting in an inadequate equilibrium between oxygen delivery and oxygen demand.

Derangements of Macrocirculation

In septic shock, the dysregulated inflammatory response, combined with increased vascular permeability, leads to a significant reduction in vascular tone, causing profound venous and arterial vasodilation. This state induces both absolute and relative hypovolemia, manifesting clinically as a sudden drop in arterial blood pressure, particularly in the diastolic component. Concurrently, venous dilation reduces the volume of stressed blood, thereby decreasing venous return and cardiac output (CO), which further impairs oxygen distribution to tissues (Monnet & Teboul, 2018b).

Clinically, the decline in ventricular preload caused by venodilation and hypovolemia is reflected by a marked reduction in central venous pressure (CVP) (De Backer & Vincent, 2018). This triggers neurohormonal compensatory mechanisms aimed at preserving adequate organ perfusion, which is closely tied to mean arterial pressure (MAP) (Augusto et al., 2011). The sympathetic nervous system activates α- and β-adrenergic receptors, enhancing heart rate and cardiac contractility. Additionally, α-adrenergic receptor-mediated vasoconstriction improves arterial tone, increasing MAP, while similar receptor activity on veins enhances venous tone, mobilizing unstressed blood into stressed volume.

These compensatory mechanisms are intended to maintain circulatory pressure. However, in septic shock, their effectiveness is significantly compromised due to adrenal insufficiency and elevated levels of vasodilatory substances, such as nitric oxide. Furthermore, intrinsic ventricular contractility is impaired in approximately 60% of septic patients, a condition known as septic cardiomyopathy. This dysfunction, which may arise at the onset of sepsis or develop

subsequently, is associated with endothelial and mitochondrial dysfunction, alterations in β-adrenergic receptors, and disruptions in myocardial calcium metabolism (Aneman & Vieillard-Baron, 2016). While septic cardiomyopathy is reversible following the resolution of sepsis, it poses a critical challenge for emergency physicians, as it diminishes the efficacy of compensatory mechanisms and therapeutic interventions.

Derangements of Microcirculation

Under normal physiological conditions, oxygen delivery (DO2) exceeds tissue oxygen consumption (VO2), with the balance reflected by central venous oxygen saturation (ScvO2) of hemoglobin. When oxygen demand increases or delivery decreases, oxygen extraction rises, resulting in a reduction in ScvO2. However, below a critical DO2 threshold, oxygen extraction cannot increase further, leading to DO2/VO2 dependency, where metabolic demands become reliant solely on available oxygen.

In septic shock, the critical DO2 threshold is higher than in other types of shock, causing a rapid decline in oxygen extraction efficiency. As a result, normal ScvO2 levels are frequently observed in septic shock patients. This phenomenon arises from various mechanisms, including microvascular abnormalities and cellular dysoxia (On behalf of the Cardiovascular Dynamics Section of the ESICM et al., 2018). Cellular dysoxia inhibits aerobic glycolysis, resulting in lactate accumulation.

Fluid Therapy

The administration of fluids, alongside antibiotic therapy, constitutes the cornerstone of initial treatment for septic shock patients. This therapeutic approach aims to correct hypovolemia by increasing stressed blood volume, thereby enhancing venous return and cardiac preload. The resultant increase in cardiac output (CO) is expected to improve oxygen delivery. However, following the initial resuscitation phase, approximately half of the patients will become non-fluid responsive. In such cases, further fluid boluses may lead to fluid accumulation, reduced oxygen delivery (DO2), and impaired venous return, ultimately worsening organ perfusion pressure (Monnet & Teboul, 2018b). To address this, various tests have been developed to predict fluid responsiveness, with the passive leg raising (PLR) test being particularly favored for its simplicity and suitability in the Emergency Department (ED) setting (Monnet & Teboul, 2015). This test involves moving the patient from a semi-recumbent position by lowering the trunk and raising the legs to a 45° angle, transferring approximately 300 mL of blood to the ventricles and increasing cardiac preload. If CO rises by at least 10% from baseline, the patient is deemed preload responsive and likely to benefit from further fluid administration. Continuous CO monitoring is recommended to assess the effects of a PLR test (Monnet & Teboul, 2018a).

It is important to note that all septic shock patients presenting to the ED should initially be considered fluid responsive and promptly treated with a fluid bolus. The 2016 SCC guidelines recommended administering 30 mL/kg of crystalloids within the first three hours, a guideline that sparked debate. Some clinicians argued that the three-hour window was too prolonged for a time-sensitive condition like septic shock, while others criticized the fluid volume as being overly generous and not universally applicable. These concerns were compounded by a lack of robust data supporting such recommendations.

The 2018 SCC bundle update addressed some of these concerns by replacing the 3- and 6-hour bundles with the hour-1 bundle, emphasizing the need for immediate treatment of septic patients. Despite this adjustment, the protocol did not incorporate personalized fluid administration, as advocated by many experts. Teboul and Monnet have recently proposed initiating fluid therapy with approximately 10 mL/kg over the first 30–60 minutes while closely monitoring the patient. They suggested reducing fluid infusion if tachypnea worsens or oxygen saturation drops. Conversely, they recommended increasing the infusion rate if low arterial

pulse pressure, prolonged capillary refill time, or persistent skin mottling are observed despite initial fluid resuscitation. This individualized approach aligns with the principle of balancing the risks and benefits for each patient while employing dynamic tests of preload responsiveness to guide ongoing fluid management.

Choice of Fluids

The 2016 SCC guidelines advocate the use of crystalloids for fluid resuscitation in septic patients. Over time, other fluid types, including synthetic colloids such as hydroxyethyl starch solutions (HES), were proposed based on the premise that they would provide superior intravascular volume expansion compared to crystalloids (Bayer et al., 2012). However, studies revealed that HES treatment was associated with increased renal damage and higher mortality rates, leading to the retraction of many articles supporting its use in sepsis. Consequently, in 2013, the European Medicines Agency (EMA) prohibited the use of HES in treating septic and critically ill patients. Retrospective analyses also indicated that the volume of crystalloids required for fluid resuscitation in critically ill patients was, on average, only 1.4 times higher than that of colloids (Schortgen & Brochard, 2012). Currently, the sole indication for HES use is limited to treating hypovolemia caused by acute blood loss when crystalloids alone are insufficient.

Regarding the choice of isotonic crystalloid solutions—balanced crystalloids versus normal saline—no definitive recommendations have been established over the years. While saline solution has been criticized for its high chloride content, which may adversely affect renal function and recovery from severe illness, no study has conclusively demonstrated the superiority of balanced crystalloids in critically ill patients. The SALT-ED study found no difference in in-hospital free days between saline and balanced crystalloids in non-critically ill ED patients but reported a significantly lower incidence of major adverse kidney events within 30 days for the balanced crystalloids group (Self et al., 2018). Similarly, the SMART trial, involving 15,802 critically ill patients, demonstrated a lower composite outcome of death, new renal-replacement therapy, or persistent renal dysfunction with balanced crystalloids (Semler et al., 2018). In the septic subgroup (n=1641), balanced crystalloids were associated with lower 30-day in-hospital mortality, reduced incidence of major renal events, and more vasopressor-free days compared to normal saline. Although no official recommendations have been issued by scientific societies, the use of Ringer's Lactate solution in septic shock resuscitation appears appropriate. Ongoing trials, including the PLUS (Plasma-Lyte 148 vs. Saline) and BaSICS (Balanced Solution vs. Saline in Intensive Care) studies, are expected to provide further evidence.

The use of hypertonic solutions in septic shock resuscitation has been questioned following the premature termination of the HYPERS2S trial, which evaluated hyperoxia versus normoxia and normal saline versus hypertonic saline, due to increased mortality in both intervention groups. Although hypertonic solutions, such as 3% NaCl, were theorized to exert greater osmotic effects, these effects are transient and accompanied by a significant chloride load, increasing the risk of renal damage. Consequently, the routine use of hypertonic saline in septic shock patients is not recommended in clinical practice.

Vasopressors

As per the Sepsis-3 definitions, septic shock patients are clinically identified by the necessity of vasoactive medications. In line with this, both the 2016 and 2018 SSC guidelines advocate for the early initiation of vasopressors in hypotensive septic patients to counteract severely impaired arterial tone (Rhodes et al., 2017).

Norepinephrine

Norepinephrine (NE) is recommended as the first-line vasopressor in the management of septic shock. Its vasoconstrictive effect is mediated through the activation of α1-adrenergic receptors, with minimal impact on heart rate (Shi et al., 2020).

The early administration of NE in septic patients has garnered increasing support over time, backed by multiple validated reasons. Primarily, by correcting hypotension or minimizing its duration—prolonged hypotension being a major determinant of mortality—patient outcomes are improved. Secondly, α1-receptor stimulation on the venous side induces venous constriction, thereby augmenting stressed blood volume, enhancing venous return, and improving cardiac preload. In this context, fluid administration becomes more efficient due to its action on a pressurized venous system, reducing the overall fluid requirement. Additionally, in the early stages of septic shock, cardiac β1-adrenergic receptors remain expressed on cardiac cells, allowing NE to enhance cardiac contractility. This benefit is further reinforced by an increase in diastolic arterial pressure, which serves as the perfusion pressure for the left ventricle coronary artery.

Several studies have examined the outcomes of early NE administration in septic shock. Retrospective studies by Colon-Hidalgo and Bai demonstrated that the timing of NE initiation is an independent predictor of mortality. The CENSER trial compared early NE administration with NE administration only after the failure of fluid therapy. It revealed that early NE use resulted in higher rates of shock control within the first six hours (primary endpoint). However, no significant differences were observed in mortality (secondary endpoint), though the early NE group experienced fewer cases of cardiogenic pulmonary edema and new-onset arrhythmias. Further clarity is anticipated from the CLOVERS trial, a large ongoing randomized controlled trial designed to assess the impact of early NE on 90-day mortality.

Current evidence, including findings from a recent meta-analysis demonstrating reductions in both short-term mortality and fluid requirements, supports the safety of early NE administration. Emergency physicians are thus encouraged to initiate NE during the early resuscitation phase, especially in patients with concurrent tachycardia and low diastolic arterial pressure, indicative of severely impaired arterial tone (Magder, 2018).

Once NE administration is initiated, it is generally agreed that its dosage should be titrated to achieve a mean arterial pressure (MAP) of 65 mmHg. However, the ideal target MAP remains unclear. The SEPSISPAM study, which compared MAP targets of 65 mmHg and 85 mmHg, found no significant differences in mortality. Nonetheless, a subgroup analysis of patients with pre-existing arterial hypertension showed improved renal function with a higher MAP target. Consequently, the European Society of Intensive Care Medicine (ESICM) task force has recommended an initial MAP target greater than 65 mmHg for septic shock patients with arterial hypertension. In cases where high NE doses (≥ 1 μg/kg/min) are required to address refractory hypotension, the addition of a second vasopressor is advised.

Other Vasoactive Agents

Vasopressin is the second-line agent recommended by the 2016 SSC guidelines for use alongside NE in refractory shock cases. By stimulating a different receptor, vasopressin reduces the reliance on adrenergic tone while enhancing vasoconstriction. A meta-analysis indicated that combining vasopressin with NE lowered the incidence of arrhythmias, such as atrial fibrillation, compared to NE alone, although mortality rates remained unchanged (Nagendran et al., 2019). However, vasopressin availability varies across countries.

Epinephrine is another second-line vasopressor recommended by the 2016 SSC guidelines, particularly in cases of concurrent cardiac dysfunction. Nevertheless, existing literature does not indicate superior survival outcomes with epinephrine alone compared to NE combined with dobutamine.

Dopamine, previously included in guidelines, is no longer recommended for managing septic patients as a vasopressor or low-dose renal protective agent. Its use has been associated with a higher risk of cardiac arrhythmias and increased mortality compared to NE. Currently, dopamine is reserved for cases of bradycardia.

Monitoring

Despite its limitations, physical examination remains a crucial component in recognizing septic shock and guiding initial management. Basic monitoring parameters, such as heart rate, peripheral oxygen saturation, urinary output, arterial blood pressure, and central venous pressure (CVP), provide valuable insights into the hemodynamic status of septic patients. These easily accessible variables enable the identification of rapid changes and help set specific resuscitation targets, such as achieving a MAP of at least 65 mmHg (Chen et al., 2020).

For patients receiving vasopressors, invasive arterial blood pressure monitoring is recommended. However, NE administration should not be delayed by the placement of arterial or central venous catheters (CVCs). In such scenarios, vasopressors can initially be administered via a peripheral venous line with non-invasive blood pressure monitoring, transitioning to CVC administration with invasive arterial monitoring as soon as feasible. Since basic hemodynamic monitoring cannot assess the impact of fluid challenges on CO, continuous CO monitoring methods are advised to track changes in CO during preload responsiveness tests and fluid challenges.

Over the last two decades, the use of pulmonary artery catheters has significantly declined, with transpulmonary thermodilution (TPTD) emerging as the new gold standard for cardiac output (CO) measurement. This technique involves the injection of three boluses of cold saline into the central venous catheter (CVC) and detecting changes in blood temperature using a femoral thermistor-tipped arterial catheter. Through this process, TPTD devices can measure CO. However, their use in septic patients is primarily recommended in cases of acute respiratory distress syndrome in intensive care units (ICUs) rather than in emergency departments (EDs) (Gavelli et al., 2020).

Consequently, numerous non-invasive methods for CO monitoring have been developed over the years. Among these, the analysis of arterial pulse wave contour, which correlates with CO, involves the placement of an arterial line with a specialized catheter. This method estimates CO using proprietary algorithms that analyze each cardiac beat while incorporating biometric parameters. However, unlike TPTD devices, this method lacks a calibration system. Over time, or in cases of altered vascular resistance, its measurements become less reliable.

Echocardiography, in contrast, is entirely non-invasive and readily available at the bedside. CO is assessed by analyzing relative changes in the velocity–time integral (VTI) of the left ventricular outflow tract. This approach enables the evaluation of beat-to-beat CO changes during tests of preload responsiveness and fluid administration, demonstrating good accuracy and inter-observer agreement. Additionally, novel techniques for non-invasive CO monitoring, such as bioreactance and plethysmography, have been developed, refined, and validated in recent years, making them potentially ideal for ED settings. However, it is important to note that variations in the inferior vena cava should not be used to evaluate preload responsiveness or fluid administration effects in spontaneously breathing patients.

Lactate and Peripheral Perfusion Assessment

The 2016 Surviving Sepsis Campaign (SSC) guidelines identify blood lactate normalization as a resuscitation target in septic shock patients, based on the assumption that elevated lactate levels indicate tissue hypoperfusion. However, as lactate levels depend on the balance between production and clearance, the normalization kinetics may be delayed during resuscitation. This process is further complicated by the possibility of hyperlactatemia due to causes other than hypoperfusion. In this context, capillary refill time (CRT)—defined as the time required for a distal capillary bed to regain its color after blanching pressure is applied—has recently gained attention as a tool to assess peripheral tissue perfusion. The ANDROMEDA-SHOCK study (2019) compared peripheral perfusion-targeted resuscitation with lactate-targeted resuscitation in 424 septic shock patients and found that, while the CRT-targeted strategy did not achieve

statistical significance ($p = 0.06$), it was associated with lower 28-day mortality. This finding has since been supported by several post-hoc analyses (Zampieri et al., 2020).

Antimicrobial Therapy

Antimicrobial therapy, along with fluid resuscitation, forms the foundation of treatment for septic patients. To avoid substantial delays in treatment initiation, antibiotic administration should ideally be preceded by appropriate microbiological cultures. Current guidelines recommend collecting two sets of blood cultures, one for aerobic and one for anaerobic organisms.

Timing of Antimicrobial Therapy

The 2016 SSC guidelines emphasize the importance of initiating intravenous antibiotic therapy within one hour of recognizing sepsis or septic shock. Multiple studies have demonstrated the adverse effects of delayed antibiotic administration in septic patients. For instance, a retrospective analysis conducted by Liu et al. involving 35,000 septic patients from 21 EDs in the United States revealed that delays in antibiotic administration significantly increased adjusted in-hospital mortality, with an odds ratio (OR) of 1.09 (1.05–1.13) for each hour of delay. The unadjusted analysis identified septic shock patients as particularly vulnerable to the detrimental effects of delayed treatment. Similarly, Seymour et al., in a retrospective study of 40,696 septic and septic shock patients, found that increased time to antibiotic administration was linked to higher risk-adjusted in-hospital mortality [OR 1.04 (1.03–1.06) per hour].

More recently, Kashouris et al. investigated the impact of the time between prescription and antimicrobial administration on mortality among 4,429 septic patients. Their findings indicated that the OR for 28-day mortality increased with delays beyond one hour, reaching a median value of 1.85 (1.29–2.65) when the delay exceeded 12 hours. Additionally, a retrospective analysis of 10,811 ED septic patients demonstrated that each hour of delay in initiating antibiotics increased the odds of in-hospital [OR 1.16 (1.07–1.26)], 30-day [OR 1.12 (1.06–1.18)], 90-day [OR 1.09 (1.04–1.15)], and one-year [OR 1.10 (1.05–1.14)] mortality (Peltan et al., 2019).

Antimicrobial Therapy Selection

Given the critical importance of timely antibiotic administration, empiric broad-spectrum antimicrobial therapy should be initiated promptly, pending identification of the causative pathogen and determination of antimicrobial sensitivities. The initial selection of antibiotics should account for several factors, including the primary infection site, prevalent pathogens and antimicrobial resistance patterns in the geographical area, and patient-specific characteristics such as age and comorbidities. However, due to the heterogeneity of conditions affecting septic patients, the 2016 SSC guidelines do not recommend specific therapeutic regimens but provide general suggestions.

Since many septic shock patients present varying degrees of immunosuppression, initial treatment should target pathogens commonly associated with healthcare-acquired infections, particularly Gram-negative bacteria. The SSC guidelines recommend starting with either a broad-spectrum carbapenem (e.g., meropenem or imipenem/cilastatin) or an extended-spectrum penicillin/β-lactamase inhibitor (e.g., piperacillin/tazobactam or ticarcillin/clavulanate). Third-generation or higher cephalosporins may also be appropriate. For enhanced effectiveness, the guidelines endorse a "multidrug therapy" approach, suggesting that combining multiple antimicrobials can provide broader coverage. In critically ill patients at high risk of infections caused by multidrug-resistant pathogens, the addition of a supplementary Gram-negative agent, such as an aminoglycoside or fluoroquinolone, is recommended to increase the likelihood of effective coverage. For suspected methicillin-resistant *Staphylococcus aureus* (MRSA)-associated sepsis, adding vancomycin, teicoplanin, or another anti-MRSA agent is advised. Additionally, for patients at high risk of invasive Candida

infections, empirical inclusion of an echinocandin (e.g., caspofungin, anidulafungin, or micafungin) is considered reasonable. In cases of uncertainty, consulting an infectious disease specialist is recommended.

Once the pathogen has been identified and susceptibility data are available, empiric broad-spectrum therapy should be de-escalated to a targeted regimen, which may be either monotherapy or combination therapy, depending on the clinical scenario (IDSA Sepsis Task Force et al., 2018).

Antimicrobial Dosing in the Emergency Department

When prescribing the first antibiotic dose in septic shock patients, emergency physicians should consider the hemodynamic alterations associated with this condition, as standard dosing may fail to achieve therapeutic targets. Factors such as increased capillary permeability, hyperdynamic circulation, and substantial fluid administration can all expand the volume of distribution for hydrophilic antibiotics (e.g., β-lactams, aminoglycosides, glycopeptides). Similarly, for highly protein-bound antimicrobials, including ceftriaxone, ertapenem, daptomycin, and teicoplanin, hypoalbuminemia can increase the unbound drug fraction, further expanding the volume of distribution and enhancing the risk of early renal clearance. Consequently, an initial loading dose approximately 1.5 times the standard dose is recommended.

To optimize antimicrobial efficacy, the pharmacokinetic/pharmacodynamic (PK-PD) index for each antibiotic class should be considered when determining maintenance doses. This may involve shortening dosing intervals or using continuous infusions. However, predicting the response to an antimicrobial regimen remains challenging due to the complex pathophysiology of septic shock. Therefore, implementing therapeutic drug monitoring for antibiotics is increasingly regarded as a standard of care in septic shock management.

Adjunctive Therapy

Corticosteroids

The rationale for administering low-dose corticosteroids in septic shock patients stems from the presence of relative adrenal insufficiency. Corticosteroids are thought to improve cardiovascular function by restoring blood volume via mineralocorticoid activity and increasing systemic vascular resistance through glucocorticoid receptor-mediated mechanisms. In 2008, the CORTICUS trial investigated the effects of hydrocortisone (50 mg IV every six hours for five days) compared to a placebo in 499 septic shock patients. While no difference was observed in 28-day mortality between patients with and without an adequate response to a corticotropin test (the primary outcome), the hydrocortisone group experienced faster shock reversal, albeit with a higher risk of superinfections. Subsequent reviews and meta-analyses have reported mixed findings. For instance, Annane et al. analyzed 12 clinical trials and found that prolonged low-dose corticosteroid therapy reduced 28-day mortality. However, Sligl et al. and Volbeda et al., reviewing 8 and 35 trials respectively, were unable to replicate these conclusions. Accordingly, both the 2012 and 2016 SSC guidelines recommend low-dose corticosteroids (e.g., hydrocortisone 200 mg IV daily) only for patients with severe shock unresponsive to fluids and vasopressors (Dellinger et al., 2013).

In 2018, two large RCTs, ADRENAL and APROCCHSS, provided additional insights. The ADRENAL trial included 3,658 septic shock patients on mechanical ventilation and assessed 90-day mortality as the primary outcome. Patients received either hydrocortisone (200 mg IV daily for seven days) or a placebo. Although hydrocortisone treatment resulted in faster shock resolution, fewer mechanical ventilation days, and shorter ICU stays, no differences were found in 90-day mortality. Conversely, the APROCCHSS trial studied 1,241 septic shock patients with poor clinical response to the 6-hour bundle of the 2008 SSC. Participants were randomized to receive hydrocortisone (50 mg IV every six hours) combined with fludrocortisone (50 μg orally once daily) for seven days or a placebo. This combination therapy significantly reduced

90-day and 180-day mortality and increased vasopressor- and organ failure-free days compared to placebo. The authors attributed the additional benefit of fludrocortisone to its mineralocorticoid potency, which potentially counteracted NF-κB-mediated downregulation of vascular mineralocorticoid receptors, further enhancing cardiovascular function. Despite conflicting results from systematic reviews and meta-analyses incorporating these trials, the 2016 SSC recommendations on corticosteroid use remain unchanged.

Ascorbic Acid and Thiamine

The potential therapeutic role of vitamin C in septic patients was initially suggested by Marik et al. in a small retrospective study, which demonstrated that intravenous administration of vitamin C in combination with thiamine and hydrocortisone (HAT therapy) reduced both mortality and organ failure in patients with sepsis and septic shock. The observed improvement in patient outcomes was attributed to the synergistic and overlapping actions of these agents on various components of the host immune response to infection, including the restoration of the dysregulated immune system (Moskowitz et al., 2018).

Since this initial study, several small-scale randomized controlled trials (RCTs) have investigated the efficacy of HAT therapy in septic and septic shock patients, with conflicting results. A meta-analysis by Rui Shi et al. failed to demonstrate a clear mortality benefit in patients treated with HAT therapy. However, it did report a significant reduction in the frequency of vasopressor use and a decrease in the Sequential Organ Failure Assessment (SOFA) score. The ongoing VICTAS Trial, which aims to enroll 2,000 septic patients, may provide more definitive conclusions on the efficacy of HAT therapy.

Conclusions

Patients with severe sepsis and septic shock are at a heightened risk of death and organ dysfunction, with substantial in-hospital mortality. Since the publication of the last SSC guidelines, numerous studies have contributed new insights into the pathophysiology and management of septic shock. However, managing septic shock remains a formidable challenge for emergency physicians, who are tasked with early detection and initiating treatment during the critical early phases. Therefore, it is crucial for emergency physicians to remain informed about recent advancements in the management of septic patients.

This narrative review serves as an updated and practical learning tool, aimed at equipping emergency physicians with essential information on the past, present, and emerging research in sepsis management.

Ultimately, we believe that a systematic approach that emphasizes the early identification of septic patients and prompt initiation of treatment has the potential to significantly reduce mortality in the emergency department (ED). To further enhance disease management, emergency physicians should tailor treatment to the specific characteristics of each patient.

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